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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,100	CARR, FRANCIS J	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-74* is/are pending in the application.

4a) Of the above claim(s) *16-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

In view of the appeal brief filed on 6/24/2005, PROSECUTION IS HEREBY REOPENED. A new ground of rejection is set forth below. [The indication of the withdrawal of the rejection under 35 USC 103 in the Advisory action mailed on 2/28/2005 is regretted. The rejection is reiterated below.)

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

Status of Claims

Claims 16-74 are pending in the application.

Claims 16-51 are withdrawn from consideration, as being drawn to non-elected invention.

Claims 1-15 have been cancelled.

Claims 52-74 are under examination.

Specification

The disclosure is objected to because of the informalities as set forth in the Office action of 8/25/2004 and reiterated as follows: There are no Seq. ID Nos. for the peptide sequences at page 3, lines 8 and 9; page 5, lines 1 and 5; page 26, line 7. Applicant should check for other peptide or nucleic acid sequences without any Seq. ID. No. in the specification.

Response to Arguments

Applicant states that a revised sequence listing will be provided in due course to reflect the sequences on pages 3, 5, and 26.

In reply, in the absence of new sequence listing, the objection to the specification has not been overcome.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 52-63 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claimed library of individual proteins, one or more of which is able to bind to a target of interests each comprising within its amino acid sequence one or more individual identifier sequence amino acid tracts which are unique to said individual proteins and are flanked by one or more protease sensitive sites would read on a naturally occurring mixtures of proteins naturally present in e.g., mammalian body. For example, mammalian proteins (i.e., antibodies) that are present in the body are known to be mixtures of proteins that naturally undergo proteolysis by protease enzymes. These antibodies are known to bind target proteins (i.e., antigens). See the e.g., Sato et al (Biochemistry) reference, newly submitted by applicant.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 52-74 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s),

at the time the application was filed, had possession of the claimed invention.

Written Description:

The specification fails to provide an adequate written description of the claimed library that encompasses a huge genus of a protein of no definite sequences/structures. The claimed library of protein that comprises one or more individual identifier sequence amino acid tracts does not recite the kind and/or length of these individual amino acid sequence tracts. Nor does it describe how it is unique from one another and/or its location in the protein sequences. Furthermore, there is no description as to the kind of protease sensitive sites and/or the protease to which the sites are considered sensitive thereto. The claim recites far too numerous variables for each of the recited variable. A "written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula [or] chemical name of the claimed subject matter sufficient to distinguish it from other materials". University of California v. Eli Lilly and Col, 43 USPQ 2d 1398, 1405(1997), quoting Fiers V. Revel, 25 USPQ 2d 1601m 16106 (Fed. Cir. 1993). See also University of Rochester v. G.D. Searle & Co., 68 USPQ2d 1424 (DC WNY 2003). The description in the specification

drawn to scFv with specific random tract and specific enzyme protease is not a description of the genus claim. Neither does the specification discloses that even for this specific species different types of enzymes can be used. There is no distinguishing definition e.g., by structure to differentiate the genus claimed to any specific or genus library. Attention is drawn to applicant's newly cited Sato reference, Exhibit 1, as discussed below.

Response to Arguments

In the Appeal Brief on page 4, applicant argues that the design of identifier sequence amino acid tracts (i.e., barcodes) including their structures is described throughout the specification. For example at page 4, lines 23-44, an eight amino acid barcode sequence using 17 of the 20 natural amino acids is described. A specific example is provided of a family of peptide barcodes and their corresponding oligonucleotide sequences. Example 2, beginning on page 29 provides a specific example.

In response, a review of the cited section page 4 does not reveal any sequence of any proteins but only a part i.e., the claimed tract. The description that the claimed tract is any 17 of the 20 naturally occurring amino acids without defining the amino acids defined by each of the letter A-Q is not a complete

description of the claimed library of a whole protein. The specific protein scFv antibody described in Example 2 is not controverted. The issue is whether this single protein is representative of the huge scope of the claimed protein library comprising different types of barcodes of no define sequences. It is not apparent how the function of the single protein species, scFv can be correlated to the huge scope of a protein such as growth hormone, viral, bacterial, tumor and etc. since these proteins differ in structure with scFv. To satisfy a written description requirement for a claimed genus a sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. A representative number of species means that the species, which are adequately described, are representative of the entire genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure indicates that the applicants have invented

species sufficient to constitute the gen[us]. Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004).

Applicant argues that the protease sensitive sites are well known in the art. It is also argued that the specification describes the structures for enterokinase, Factor Xa and thrombin cleavage sites. Applicant states that Exhibit 1 discloses other protease sites known in the art. A patent need not teach, and preferably omits, what is well known in the art.

In reply, as stated by applicant, protease acts on ***sensitive sites***. However, it is not apparent from the claimed unstructured protein, the sites that are sensitive to an enzyme. Neither is it apparent whether the undefined site is the only site that is sensitive to an enzyme. Exhibit 1 (Eaton et al), like the specification, describes a single protein, factor VIII cleaved by thrombin, APC and Factor Xa. In the abstract at page 505, Eaton discovers that with this single protein one of the enzymes activates and inactivates factor VIII. At page 506, Eaton states, "…other than species differences, the reasons for this discrepancy is (are) unknown……." Further, at page 507, col. 2, first incomplete paragraph, Eaton states "…..the site at which this cleavage occurs has yet to be determined…" Clearly

the art, at the time of applicant's invention, like the specification describes studies for single or specific protein having definite structure. Even with the single protein having a defined structure, Eaton indicates that there are discrepancies of results obtained from one enzyme to another. What more for a collection of millions of unstructured proteins, as claimed?. A true test of any prior art relied on to show or suggests that a chemical compound is old i.e., known in the art, is whether the prior art is such as to place the disclosed "compound" in the possession of the public. If merely listing compounds could suffice as a disclosure, it would bar patent protection to the person who actually discovered a compound on the list and, in so doing, thwart the Constitutional purpose of the patent system. See in re Wiggins, 488 F.2d 538, 179 USPQ 412(CCPA 1973). A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. In biotechnological invention one cannot necessarily claim a genus after only describing a single species because there may be unpredictability in the results obtained from species other than those specifically described. Refer to the Sato reference, above.

Applicant relies on the recent Federal Circuit decision - Capon et al v. Eshhar et al v. Dudas that applicant believes is relevant to the instant application. The decided claim is stated to essentially fail to recite specific protein sequence information in the claims or the specification.

In reply, the fact situation in the Capon case is not similar to the instant case. The claimed invention claims a library (mixtures) of numerous combinations of different proteins including but not limited to antibodies, antigens (e.g., viral, bacterial, tumor and etc.), enzymes, growth factors and other unnamed or unstructured proteins. This is but one of the many undefined structures of the genus claim. Thus, the infinite variables of the claimed library cannot be completely described by the single protein species, scFv antibody in the specification.

C). ***Scope (Enablement) Rejection:***

Claims 52-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for scFv with specific barcodes and enzyme, does not reasonably provide enablement for any type of proteins, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected,

to make and use the invention commensurate in scope with these claims.

The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the scope (enablement) requirement and whether any necessary experimentation is "undue" include:

(1) the breadth of the claims,
(2) the nature of the invention,
(3) the state of the prior art,
(4) the level of one of ordinary skill;
(5) the level of predictability in the art,
(6) the amount of direction provided by the inventor,
(7) the existence of working examples, and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, (U.S.P.Q. 2d 1400 (CAFC 1988).

1). The specification fails to give adequate direction and guidance in how to readily go about determining the kind, number and length of tract of amino acid within any type of protein that can be cleaved by an enzyme, the type of enzyme that cleaves a protein, the kind of proteins (or tracts) that retains its capability of binding to a target when proteolyzed.

2). The specification failed to provide working examples for the broad scope of the claimed library and method. Example 2 of the working example describes only a scFv with a random tract cleave by a V8 protease.

3). The breadth of the claims encompasses a large diversity of protein library with an amino acid sequence tracts, proteases and the predetermined sites of variations in the amino acid tract. It is well known in the art, that it is often difficult to know where a protease cleaves a protein. Too often an enzyme cleaves a protein at a different site, rather than at the intended site, resulting in an inactive cleaved protein. See Sato above.

4). The state of the prior art is such that techniques are applied specifically for a predetermined protein with specific mutations thereof, if any, and target protein.

5). The art is inherently unpredictable because it is not possible to predict which predetermined amino acid tract would be cleaved by an enzyme having the ability to bind to its target. It is generally known that the conformational freedom that promotes binding, e.g., by modifying the peptides into the protein sequences, might be restricted which may likely perturb the function and stability of the protein in ways difficult to predict and measure. Some proteins accommodate insertions (variations) at numerous sites throughout their primary sequence. Others are much less accommodating. It is difficult in general to predict which proteins are robust to insertions, and which sites in a particular protein are best suited to insertion of multiple independent sequences. The complex spatial

configuration of amino acid side chains in proteins and the interrelationship of different side chains in the randomized sites are insufficiently understood to allow for such predictions. Selective (site-directed) mutagenesis and saturation mutagenesis are of limited utility for the study of protein structure and function in view of the enormous number of possible variations in complex proteins. There are still no rules that have emerged that allow structure to be related to sequence in any simple fashion (even as applied to the actual compounds).

6). Because the art is unpredictable, applicants' specification reasonably would not have assured persons skilled in the art that the numerous amino acid tract in a protein would result in a protein library that binds to a target of interest without undue experimentation. Applicants do not adequately enable persons skilled in the art to readily determine such. Applicants need not guarantee the success of the full scope of the claimed invention. However, skilled artisans are provided with little assurance of success.

The language of the claim is so broad that it causes claim to have a potential scope of protection beyond that which is justified by the disclosure.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 52-56, 58, 64-69 and 74 rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al (The Jrnl. of Biol. Chemistry).

Chen discloses at page 23309, Fig. 1 a library comprising of a thrombin receptor's amino terminal exodomain fused to a

transmembrane domain to display potential tethered agonists. The peptide SFLLR on the thrombin receptor has been replaced with random pentapeptide sequence (individual sequence tracts, as claimed) so that cleavage of the library by thrombin (protease sensitive sites) unmasks a set of potential tethered peptide agonists. When co-expressed with a target receptor, a member of the library bearing a tethered ligand sequence activates the target receptor. See the Experimental Procedures at page 23398 and Results and Discussion section starting at page 23399. Accordingly, the specific library of Chen comprising thrombin receptor with an amino terminal exodomain that is proteolyzed by an endopeptide containing random pentapeptide sequences fully meet the broad claimed library having no definite structure/ sequence(s).

Claims 52-57, 61, 64-70 and 74 are rejected under 35 U.S.C. 102(b) as being anticipated by Matthews et al (Science).

Matthews discloses at e.g. page 1113 up to page 1116, specifically Fig. 1 a library of proteins with a library of random peptide, Table 1 inserted between the protein hGH and phage. At page 1114 a method for identifying protease substrates from a library of possible peptide sequences is described. The method involves constructing a library of

fusion proteins containing an amino terminal domain used to bind to an affinity support followed by a randomized protease substrate sequences and the carboxyl terminal domain of M13 gene 111.Each substrate sequence is displayed on phagemid particles between a human growth hormone that binds to the hGH-binding protein and a truncated form of the gene III protein. The phage library is disclosed at page 114, col. 2 and Factor Xa. Accordingly, the library and method of Matthews that recites specific protein with the specific library fully meet the broad claimed library and method using a library of no defined structure/sequence.

Claims 52-55, 58-69 and 73-74 are rejected under 35 U.S.C. 102(e) as being anticipated by Georgiou (USP 5,866,344).

Georgiou discloses at Example 3, a construct comprising scFv (digoxin) modified by incorporating a protease cleavage site. For example, the recognition sequence of enterokinase [(Asp)4 -Ile-Arg] can be introduced in the Lpp-OmpA(46-159)-scFv between the OmpA(46-159) and the scFv domains. The protease cleavage site at the N-terminal of the scFv antibody domain of the fusion protein is then used to release the scFv antibody in soluble form following treatment of the cells with the appropriate proteolytic enzyme. Because the outer membrane of E. coli serves as a

protective barrier to the action of externally added protease, very few contaminating proteins will be present in the culture supernatant. A single colony expressing a desired single chain Fv antibody can be grown in liquid media and harvested by centrifugation after overnight growth at 24.degree. C. The cells are resuspended in buffer to maintain the pH approximately neutral. Protease added at appropriate concentrations to the fusion protein to be treated and incubated at least 4 hours at 4.degree. C. will release the soluble single chain Fv. Subsequently the cell suspension is centrifuged and the supernatant containing the solubilized single chain Fv antibody is collected. Georgiou further disclose screening for antibodies employing the methods that allows one to select an antibody or antibody fragment from a plurality of candidate antibodies that have been expressed on the surface of a host cell. Genes for antibody fragments may also be generated by semisynthetic methods known in the art (Barbas et al., 1992). Using the conserved regions of an antibody fragment as a framework, variable regions can be inserted in random combinations one or more at a time to alter the specificity of the antibody fragment and generate novel binding sites, especially in the generation of antibodies to antigens not conducive to immunization such as toxic or labile compounds. Along the same lines a known antibody sequence may be

varied by introducing mutations randomly or site specifically. This may be accomplished by methods well known in the art such as mutagenesis with mismatched primers or error-prone PCR. The use of random mutagenesis to create an antibody library is also disclosed. Such a library might include antigen binding domains of a known antibody or antibodies that have catalytic properties. See also, col. 4, line up to col. 14, line 37.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 52-70 and 73-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knappik (USP 6300064) in view of either Ring (USP 5,849,877) or Markland et al (WO 92/15679) for reasons of record and reiterated below.

Knappik discloses e.g., abstract, a library of antibody (protein, as claimed) with synthetic consensus sequences (individual amino acid sequence tracts) having protease cleavage sites. Knappik discloses at col. 7, line 60 up to col. 13, line

3 that the complete collection of (poly)peptide sequences represent the complete structural repertoire of the collection of homologous proteins. These artificial (poly)peptide sequences are then analyzed, if possible, according to their structural properties to identify unfavorable interactions between amino acids within said (poly)peptide sequences or between said or other (poly)peptide sequences, for example, in multimeric proteins. Such interactions are then removed by changing the consensus sequence accordingly. The (poly)peptide sequences are then analyzed to identify sub-elements such as domains, loops, helices or CDRs. The amino acid sequence is backtranslated into a corresponding coding nucleic acid sequence which is adapted to the codon usage of the host planned for expressing said nucleic acid sequences. A set of cleavage sites is set up in a way that each of the sub-sequences encoding the sub-elements identified as described above is flanked by two sites which do not occur a second time within the nucleic acid sequence. This can be achieved by either identifying a cleavage site already flanking a sub-sequence of by changing one or more nucleotides to create the cleavage site, and by removing that site from the remaining part of the gene. The cleavage sites should be common to all corresponding sub-elements or sub-sequences, thus creating a fully modular arrangement of the sub-sequences in the nucleic

acid sequence and of the sub-elements in the corresponding (poly)peptide. Knappik further discloses sets up two or more sets of (poly)peptides (i.e., library), where the cleavage sites are not only unique within each set but also between any two sets. The libraries comprises for example, but not limited to, two domains from antibodies such as VH or VL or two extracellular loops of transmembrane receptors. Moreover, Knappik discloses libraries of antibodies or antibody fragments, preferably single-chain Fv, or Fab fragments, which may be used as sources of specificities against new target antigens. A method for identifying one or more genes encoding one or more antibody fragments which binds to a target, comprising the steps of expressing the antibody fragments, and then screening them to isolate one or more antibody fragments which bind to a given target molecule is also disclosed. An scFv fragment library comprising the combination of HuCAL VH3 and HuCAL V.kappa.2 consensus genes and at least a random sub-sequence encoding the heavy chain CDR3 sub-element is screened for binding antibodies. If necessary, the modular design of the genes can then be used to excise from the genes encoding the antibody fragments one or more genetic sub-sequences encoding structural sub-elements, and replacing them by one or more second sub-sequences encoding structural sub-elements. The expression and screening steps can

then be repeated until an antibody having the desired affinity is generated. Knappik also discloses a method in which one or more of the genetic subunits (e.g. the CDRs) are replaced by a random collection of sequences (the library) using the said cleavage sites. Since these cleavage sites are (i) unique in the vector system and (ii) common to all consensus genes, the same (pre-built) library can be inserted into all artificial antibody genes. The resulting library is then screened against any chosen antigen. Binding antibodies are selected, collected and used as starting material for the next library. One or more of the remaining genetic subunits are randomized as described above. See further the EXAMPLES at col. 15, line 50 up to col. 28, line 60. Knappik further discloses at col. fusion proteins by providing for a DNA sequence which encodes both the (poly)peptide, as described above, as well as an additional moiety. The additional moiety may confer on its (poly)peptide partner a means of detection and/or purification. For example, the fusion protein could comprise the modified antibody fragment the additional moieties such as the commonly used C-myc and FLAG tags (Hopp et al., 1988; Knappik & Pluckthun, 1994).

Knappik fails to disclose that the endoprotease is Factor Xa as in claim 57. However, Ring discloses at col. 34, line 65 up to col. 35, line 25 the proteolytic cleavage of an isolated

sFv from its leader sequence fusions to yield free sFvs, which can be renatured to obtain an intact biosynthetic, hybrid antigen-binding site. The cleavage site preferably is immediately adjacent to the sFv polypeptide and includes one amino acid or a sequence of amino acids exclusive of any one amino acid or amino acid sequence found in the amino acid structure of the single polypeptide chain. The cleavage site preferably is designed for specific cleavage by a selected agent. Endopeptidases are preferred. Many useful cleavage agents, for instance, blood coagulation Factor Xa and enterokinase recognize and preferentially or exclusively cleave at particular cleavage sites. Useful enzymes recognize multiple residues as a cleavage site, e.g., factor Xa (which recognizes a four amino acid sequence of Ile, Glu, Gly and Arg residues, respectively), or enterokinase (which recognizes a five amino acid sequence having four Asp residues, and one Lys residue, respectively). Markland discloses at page 21, lines 5-20 that display peptides having high affinity for the target may be quite difficult to elute from the target, particularly a multivalent target. One can introduce a cleavage site for a specific protease, such as Factor Xa, into the fusion protein so that the binding domain can be cleaved from the genetic package. Such cleavage has the advantage that all resulting phage have

identical coat proteins and therefore are equally infective. The step allows recovery of valuable gene which might otherwise be lost. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use protease digestion in the library of Knappik, specifically Factor Xa for the advantage provided by e.g., Markland above. Such advantage would motivate one having skill in the art since this advantage provides for the recovery of valuable genes which might otherwise be lost if protease cleavage is not used.

Claims 71 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knappik in view of Markland or Ring as applied to claims 52-70 and 73-74 above, and further in view of Hutchens (USP 6734022).

Knappik is discussed above. Knappik does not disclose mass spectrometry i.e., MALDI-Tof determination of the peptide sequence. Hutchens discloses at col. 5, line 35 up to col. 6, line 60 a method for desorption and ionization of analytes in which unused portion of the analytes contained on the presenting surface remain chemically accessible, so that a series of chemical and/or enzymatic or other treatments (e.g., discovery of analyte-associated molecules by molecular recognition) of the analyte may be conducted on the probe tip or other presenting surface, in situ, followed by sequential analyses of the

modified analyte by mass spectrometry. In one case (i.e., repetitive sequential analyses) the analyte is adsorbed to the sample presenting surface and can be treated (modified in situ after the excess free matrix is removed (i.e., washed away). Matrix can be added back before analysis by mass spectrometry. Using this procedure, an analyte can be repeatedly tested for a variety of components by removing one matrix, modifying the analyte sample, re-applying the same or different matrix, analyzing the sample, etc. or groups of biological or other macromolecules under investigation, or subsequent examination (e.g., quantification and/or structure elucidation) by mass spectrometry. This has the advantage of achieving both the purification of the analyte sample previously required and the effect of concentrating the analyte. It reduces by a factor of 1,000 to 100,000 the amount of analyte needed for the mass spectrometry examination, since only the macromolecules which attach to the biospecific affinity reagents are removed from the analyte sample, and these can be sequestered on predetermined areas of the probe tips or sample plates that are even less than the laser spot size.

It would have been obvious to one having ordinary skill in the art to use MALDI-Tof in the method of Knappik for the

advantage taught by Hutchens. The advantage, supra, would motivate one having ordinary skill in the art.

Response to Arguments

Applicant argues in the REMARKS of 1/25/2005 that Knappik does not describe protease cleavage sites. They expressly define "cleavage site" at Column 14, lines 11-14 as being a DNA cleavage.

In reply, Knappik discloses at col. 11, lines 8-40 FLAG tags referring to e.g., Hopp et al., newly submitted by applicant which recite enzymatic cleavage using enterokinase. Furthermore, at col. 14 Knappik also translates the DNA to its corresponding polypeptide. It would be within the ordinary skill in the art to use the corresponding protease since Knappik discloses the DNA encoding protein. As stated by applicant above the protease sensitive sites is well-known in the art. The prior art cited by applicant, inter alia, Hopp, also cited by Knappik, discloses other protease sites known in the art.

Applicant further argues that there would have been no motivation coupled with an expectation of success to have modified the prior art to arrive at the present invention in view of the teaching of Knappik as teaching away from the modification. For example, on Column 19, lines 17-20 of the

Knappik patent, it is stated, in the case of V1, a few amino acid exchanges were introduced in some of the chosen germline CDRS in order to avoid possible protease cleavage sites as well as possible structural constraints.

In reply, it is not clear how this is a teaching away from Knappik. Knappik expressly stated that in order to avoid possible protease cleavage sites from the intended unique cleavage sites, then a few amino acid exchanges were introduced in some of the chosen germline CDRS. Thus, this is protecting the intended unique cleavage site from being cleaved by an enzyme other than the intended site. Applicant's argument is not commensurate in scope with the claims since the claims do not recite any amino acid residues.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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tdw
November 10, 2005

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